UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/158,272	09/22/1998	VINCENTE DIAS	10806-64	3752

7590 06/17/2002

DINSMORE & SHOHL
1900 CHEMED CENTER
255 EAST FIFTH STREET
CINCINNATI, OH 45202

EXAMINER	
WOITACH, JOSEPH T	
ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 06/17/2002 22

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/158,272	Applicant(s) DIAS ET AL.	
	Examiner Joseph T Woitach	Art Unit 1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 March 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *27,28,31-33,35-50,52-57 and 59-63* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *27,28,31-33,35-50,52-57 and 59-63* is/are rejected.

7)☒ Claim(s) *27,28,31-50 and 52* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

This application filed September 22, 1998, claims benefit of provisional application 60/062,994, filed October 23, 1997, and claims priority to foreign application 9703663-6 filed October 8, 1997 in Sweden.

The office action mailed June 5, 2002, paper number 21, has been **vacated** in favor of the action set forth below. The office action summary sheet indicated that the action was final, however the paragraph indicating that the action was final was not included in the conclusion of the action. For clarity of the record, a new office action is being mailed including the paragraph indicating finality of the action. Examiner wishes to apologize for any inconvenience that this may have caused Applicant.

Applicants' amendment filed March 11, 2002, paper number 19 has been received and entered. The specification has been amended. Claim 58 has been canceled. Claims 27, 28, 32, 33, 35-44, 50, 52, 53, 55-57 and 59-60 have been amended. Claims 61-63 have been added. Claims 27, 28, 31-33, 35-50, 52-57 and 59-63 are pending and currently under examination.

Specification

The objection to the disclosure because the specification contains sequence listings which do not have a SEQ ID NOs is withdrawn.

Applicants have submitted the necessary materials (raw sequence listing entered as paper number 20) and made the appropriate amendments to the specification regarding the polynucleotide sequences present in the disclosure. The application is now in sequence compliance.

Claim Objections

The claims stand objected to for being drawn to a non-elected invention.

Applicants note the claims have been amended and now encompass the elected invention. See Applicants amendment, top of page 9. Applicants' arguments have been fully considered but not found persuasive.

It is noted that Applicants had elected group I, claims 27, 28, 31-50 and 52, drawn to drawn to methods of genetic modification in transgenic animals (see restriction requirement page 2, paper number 5 and Applicants' election filed December 13, 1999, paper number 6). The claims as presently amended are drawn to 'mediating transgenic recombination' however the claims are not limited to transgenic animals. Presently the claims encompass recombination in eukaryotic cells in order to mediate recombination claim 27 lines 3 and 8). The methods claims as amended still encompass each of the groups set forth in the restriction requirement including genetic modification in plants (group II); genetic modification in microorganism, if the organism is eukaryotic (group III); and methodology of gene therapy (group IV) because recombination can be used for the introduction of a transgene. It is suggested that the claims be amended to more

clearly indicate the elected invention, including recitation in the preamble and specific method steps to clearly indicate that the methods are drawn to generating transgenic animals.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 27, 28, 31-33, 35-50 and 52-60 stand rejected and claims 61-63 are newly rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of mediating intramolecular recombination between two *six* sites in a mouse, comprising providing a transgenic mouse whose genome contains two *six* sites target sequences in a gene of interest in said genome, administering beta recombinase, wherein the administration of beta recombinase results in the recombination between the two *six* sites, does not reasonably provide enablement for the practice in all animals.

Applicants summarize the basis of the rejection and the nature of the instantly claimed method. Applicants argue that the manipulation of genes is known to one of ordinary skill in the art, and there is no evidence of record which demonstrates that the instantly claimed methods of incorporating beta recombinase would not work equally as well as other gene manipulation techniques which have been used in animals other than mice, such as pigs. Applicants point to working examples in the present disclosure of transfected eukaryotic cells in culture for

demonstration that beta recombinase is clearly capable of functioning in eukaryotic cells, and argue that there is no requirement for additional cofactors. See Applicants' amendment, pages 9-13. Applicants' arguments have bee fully considered but not found persuasive.

Examiner agrees with Applicants summary of the basis of the rejection and summary of the teachings in the present disclosure. Further, Examiner agrees that the specification does not have to teach what is well known in the art. Applicants have pointed to the similarities of the instantly claimed methods and those previously described for Cre/lox and Flp/frt, noting that one of ordinary skill in the art could extend the methodology for these systems for use of beta recombinase. Examiner would agree, noting that the specification clearly relies on the art for the specific details necessary for practicing the instantly claimed method to generate transgenic animals. Because the present disclosure relies on the teachings of others for practice of the claimed methods, the disclosure is also subject to the same limitations recognized in the art. Applicants have asserted in arguments that the beta recombinase system could be extended for use in other animals besides mice, such as pigs, however at the time of filing Cre and Flp have not been successfully used in pigs. As noted in the previous office action, the specification teaches specifically that beta recombinase can mediate a recombination event between two *six* sites in eukaryotic in the presence of the proper cofactor(s), however a necessary feature of the invention is the requirement of the two *six* sites present in the DNA, and the only methodology known for the targeted introduction of sequences into a gene of interest, and the subsequent generation of a transgenic animal is through the use of embryonic stem cells. The basis of the

instant rejection is the failure of the instant specification and the art to teach embryonic stem cells for the generation of a transgenic animal other than that for the mouse. The specification is silent with respect to other methodology for introducing *six* sites into a gene of interest besides through homologous recombination in embryonic stem cells, and presently, to produce an animal in which the desired gene has been disrupted through homologous recombination, embryonic stem (ES) cells are necessary. Currently, only ES cells for the mouse are available (reviewed in Seamark and Moreadith *et al.*). There is no guidance in the instant specification, nor the art of record, for the use of appropriate vectors, the specific promoter sequences or cloning details for breadth of any eukaryotic cell in the context of a transgenic animal, nor operable methods to create any transgenic animal besides the transgenic mouse. The present application has defined a novel function for beta recombinase in eukaryotic cells, and proposes the use of the beta recombinase in methodology previously described for different but related recombination systems such as CRE/lox and FLP/frt. However, neither the instant specification, nor the art of record, has resolved the many complexities involved in targeting inverted repeat sequences, such as the *six* site sequences, to the gene of interest through homologous recombination in all animals without the use of embryonic stem cells.

Additionally, the claimed methodology requires that beta recombinase be provided to the eukaryotic cell. The means of or route of administration for providing the beta recombinase is not specifically recited, however at least one means contemplated is through the expression as a transgene. It is noted that the physiological art in general is acknowledged to be unpredictable

(MPEP 2164.03). This is particularly true in the art of transgenic animals with respect to transgene behavior. Without evidence to the contrary, transgene expression in different species of transgenic animals is not consistent and varies according to the particular host species. This observation is specifically supported by Hammer *et al.* report the production of transgenic mice, sheep and pigs; however, only transgenic mice exhibited an increase in growth due to the expression for the gene encoding human growth hormone (pages 276-277, Subsection: Effect of Foreign GH on Growth). The observation is further supported by Mullins *et al.* who report on transgenesis in the rat and larger mammals. Mullins *et al.* state that "a given construct may react very differently from one species to another" (page S39, Summary). Wall *et al.* further report that "transgene expression and the physiological consequences of transgene products in livestock are not always predicted in transgenic mouse studies" (page 2215, first paragraph). In the instant case, there is no clear teaching on the level of expression of beta recombinase needed to mediate the recombination event between two *six* sites in a eukaryotic cell. Since the applicants have not disclosed all the nucleic acids encompassed by the claims, there is no way to predict efficiency nor expression of a transgene.

Finally, the specification and the art of record clearly teach that cofactors are necessary for beta recombinase to mediate a recombinant event. As detailed in the specification and the previous office action, the necessity of HMG1 in mammalian cells or HU and/or Hbsu from a prokaryotic source is absolute for the resolution of the recombination event catalyzed by beta recombinase. As taught by Alonso *et al.*, the Hbsu is required for the resolution and DNA

inversion mediated by beta recombinase (JBC, page 938). Substitution of HU from *E. coli* or of mammalian HMG1 for Hbsu functions *in vitro* as a chromatin associated protein affecting recombination (Mol Bio, page 471), however in the absence of either of these three factors, recombination does not occur (JBC, page 2943). While HMG1 may exist in other mammalian sources, the specification and the art of record is silent to whether HMG1 or a functional homolog exist in species other than mammals. Further, while Hbsu, HU or HMG1 could theoretically be supplementally supplied, the instant methods do not recite such an active step. In addition, while the specification and art teaches that these cofactors are required for beta recombinase activity, the specification is silent on the amounts or levels of expression if supplied as a transgene of these cofactors which are required to effectively act as cofactors. The instant specification and the art of record teaches that specific chromatin cofactors are required for beta recombinase activity, however it fails to provide a nexus with the necessary guidance which enables the artisan to supply these cofactors in effective amounts resulting in beta recombinase activity in transgenic animals.

While the methodology to create transgenic mice is routine, the creation of any transgenic animal is not. In particular, no ES cell for animals other than mice exists to date, so the creation of animals which depend on homologous recombination are not enabled in the art. Further, while methods for the introduction of a gene are routine, the expression of the gene and resulting phenotype of the animal is not. Without an actual reduction to practice, it is possible to predict

that introduction of a transgene or an alteration to a gene would result a predictable phenotype or even in a viable animal.

Thus, in view of the lack of guidance, working examples, breadth of the claims, the level of skill in the art and the state of the art at the time of the claimed invention was made, it would have required one of skill in the art undue experimentation to practice the invention as claimed, and therefore, the rejection is maintained.

Claims 27, 28, 32, 53 and 55 previously rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention is withdrawn.

Amendments to the claims to specifically recite the target sequences have obviated the basis of the rejection.

Claims 27, 28, 32, 53 and 55 are newly rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed.

The claims have been amended to recite 'modified versions (of natural six sites) that allow recombination activity', however the instant disclosure does not provide the necessary

written description for what modifications of the natural sites can be made and still be functional. It is noted that the instant specification provides literal support for this amendment (page 3), however it does not provide the necessary guidance wherein one of ordinary skill in the art could clearly define a functional modified version of a six site. The specification and the art of record clearly teach that beta recombinase can use only the polynucleotide sequences set forth as the *six* site sequence. Presently, in order to practice the invention as claimed the artisan must be in possession of the appropriate target sequence for beta recombinase to bind and affect recombination. The specification describes methods of using beta recombinase and the requirement of target sequences for targeting recombination, however, the only target sequence disclosed is the *six* site. However, the specification fails to provide any other sequence besides the *six* site sequence as a target sequence for beta recombinase. The claimed invention as a whole is not adequately described if the claims require essential or critical elements which are not adequately described in the specification and which are not conventional in the art as of Applicants effective filing date. Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics (as it relates to the claimed invention as a whole) such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. *Pfaff v. Wells Electronics, Inc.*, 48 USPQ2d 1641, 1646 (1998). In the instant case, the claimed embodiment of modified target sequences needed to make and use the invention as claimed lack a written description. The specification fails to describe any polynucleotide

encompassed in the claims with particularity to indicate that Applicants had possession of the claimed invention beyond the target *six* site sequence. Further, the specification fails to describe methods to establish any other sequence besides the *six* site. The written description of a claim is evaluated on the basis of the claimed invention as a whole. Case law established that the requirement for written description relates to the subject matter defined by the claims. *In re Wright*, 9 USPQ2d 1649 (Fed. Cir. 1989). To this end, while *six* site sequences meet the written description, no other specific sequence which meets the limitation of functioning as a target site for beta recombinase is adequately described or shown to exist. Thus, the specification fails to demonstrate possession of the invention as claimed. The skilled artisan cannot envision the detailed structure of the claimed target sequences except the *six* site sequence, and thus, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method. Case law has established that one cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111 (Fed. Cir. 1991), clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" *Vas-Cath Inc. v. Mahurkar,* 19USPQ2d at 1117. The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed."*Vas-Cath Inc. v. Mahurkar*, 19USPQ2d at 1116. Adequate written description requires more than a mere statement that it is part of the invention

and reference to a potential method of isolating it. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991). One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence. Analogously, in the instant case, the specification only provides for natural six sites and does not provide any written description for any other funtional modified version.

Therefore, the polynucleotide sequences needed to make and use the claimed invention do meet the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 27, 28, 31-33, 35-50, 52-57, 59 and 60 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn.

Amendments to the claims have obviated the basis of the specific rejections.

Conclusion

No claim is allowed. Claims 27, 28, 31-33, 35-50, 52-57 and 59-63 are free of the are of record because the art fails to teach the use of beta recombinase in the generation of transgenic animals. Applicants were the first to describe the properties of beta recombinase as a member of the resolvase/invertase family of recombinases. While other recombinases (Cre and Flp) have been used in the art to generate transgenic animals, these recombinases are from the Int family of recombinases and do not require additional cofactors. Beta recombinase was isolated from a prokaryotic cell and requires the cofactor Hbsu to affect recombination between two *six* site target sequences. Applicants are the first to demonstrate that in the presence of the mammalian cofactor HMG1, beta recombinase is capable of generating an intramolecular recombination event between two *six* sites in mammalian cells, and thus, as other previously described recombinases, would be useful in the generation of transgenic mammals.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period

will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph Woitach whose telephone number is (703)305-3732.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached at (703)305-4051.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist Pauline Farrier whose telephone number is (703)305-3550.

Papers related to this application may be submitted by facsimile transmission. Papers should be faxed via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center numbers are (703)308-4242 and (703)305-3014.

Deborah Crouch

DEBORAH CROUCH
PRIMARY EXAMINER
GROUP 1800/1630

Joseph T. Woitach